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An Inquiry

INTO

SOME POINTS IN UTERINE AND OVARIAN PHYSIOLOGY

AND

PATHOLOGY IN RABBITS.

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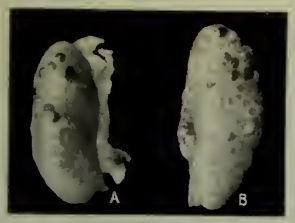

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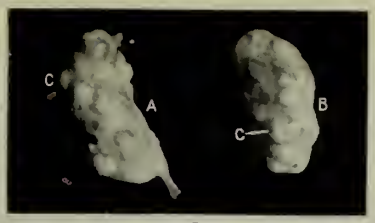

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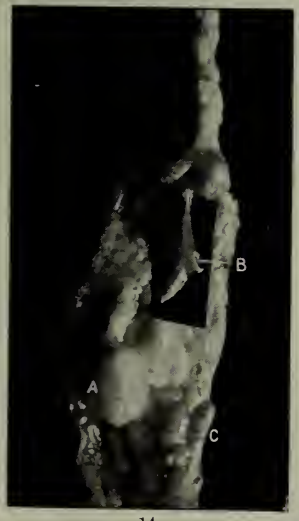

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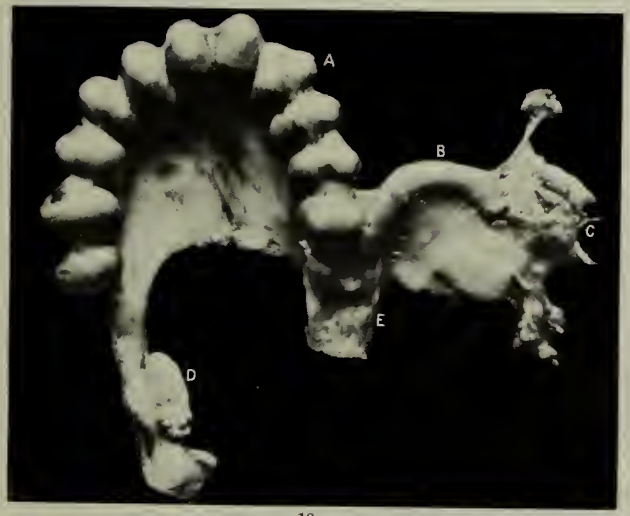

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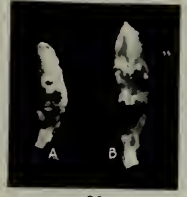

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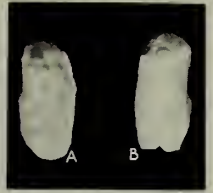

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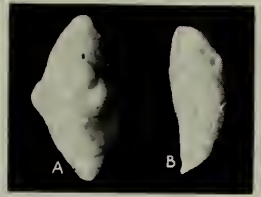

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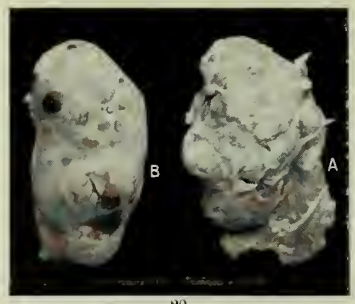

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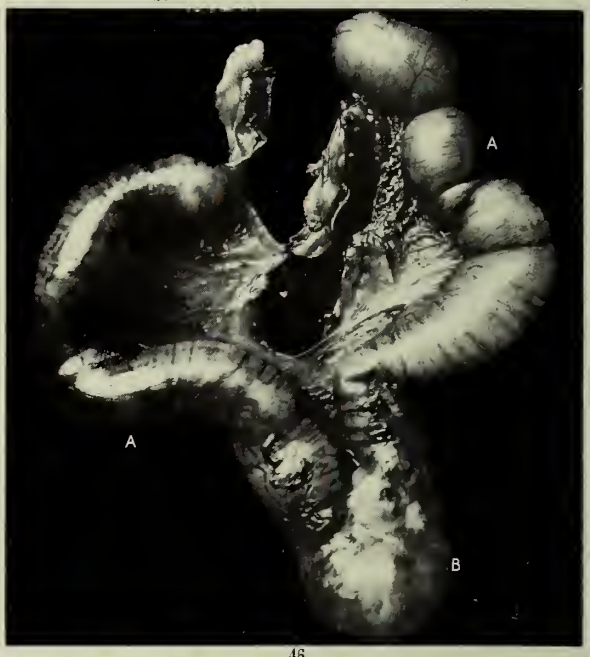

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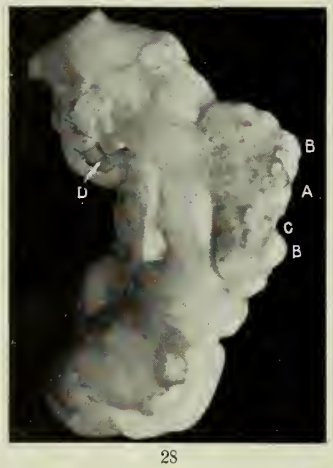

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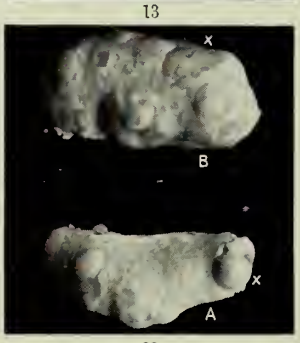

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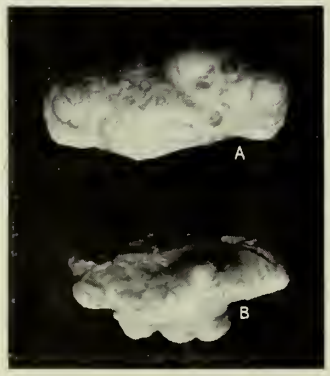

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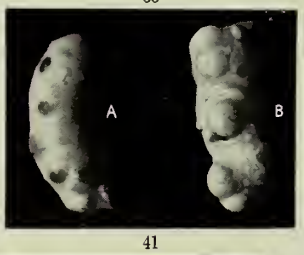

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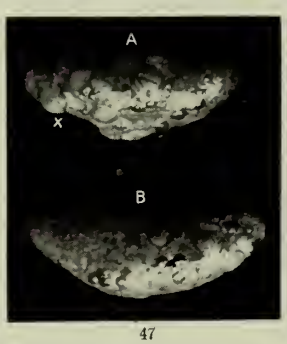

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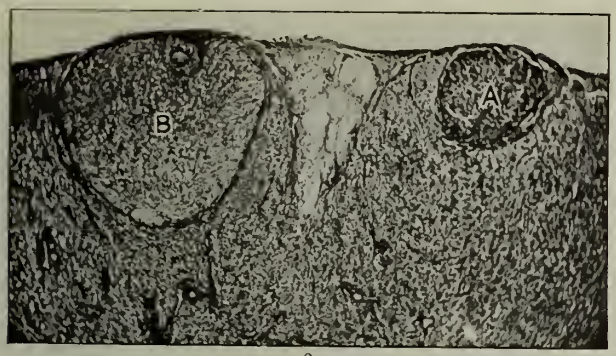

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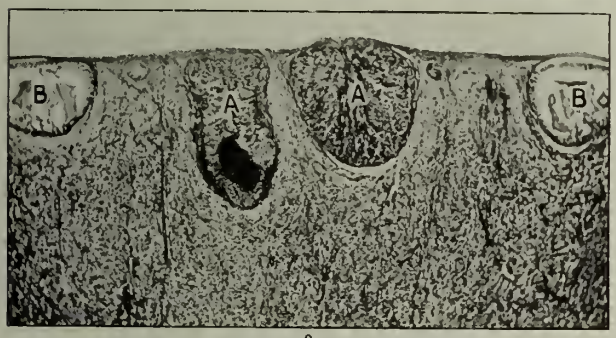

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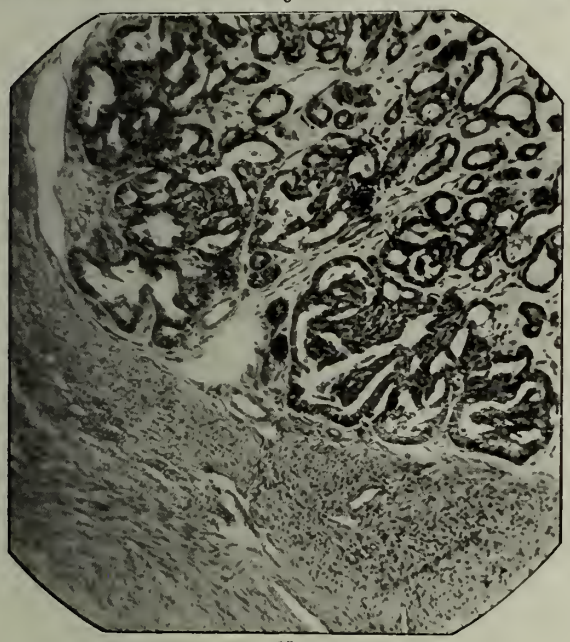

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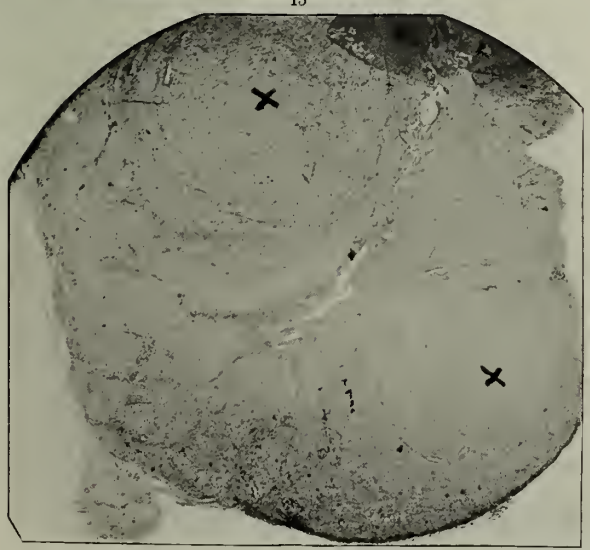

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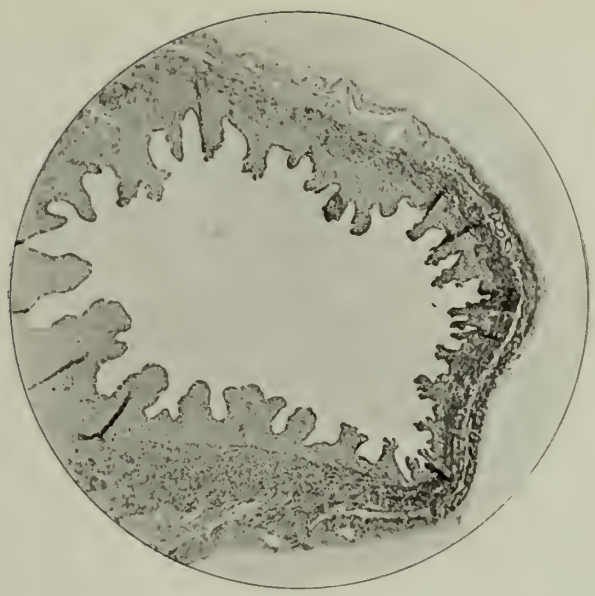

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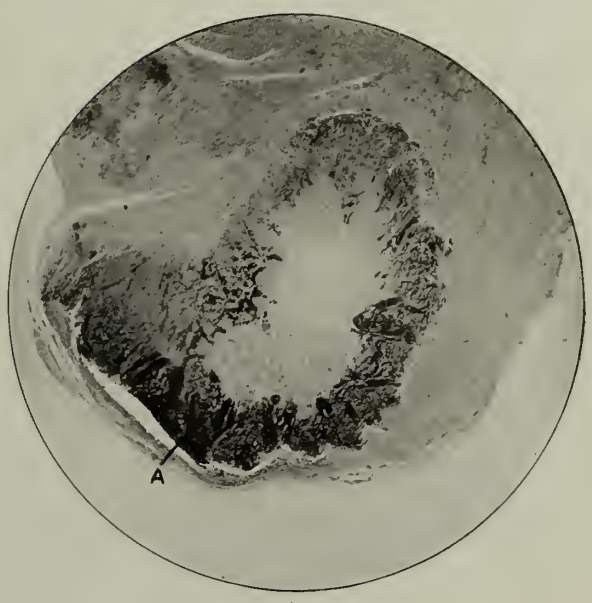

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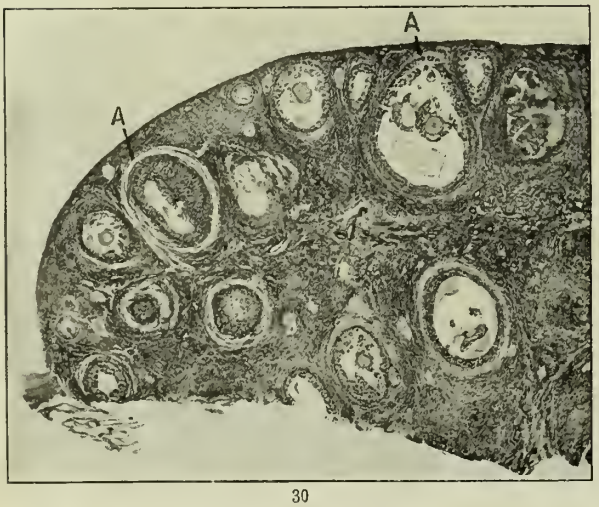

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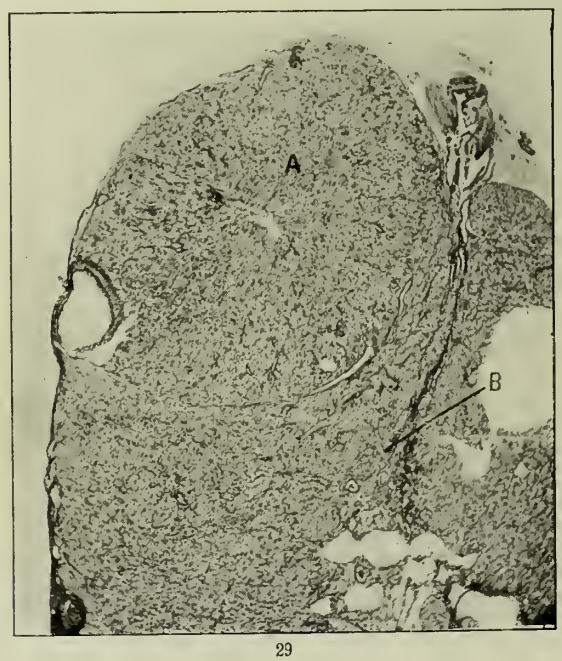

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An Inquiry

INTO

SOME POINTS IN UTERINE AND OVARIAN PHYSIOLOGY AND PATHOLOGY IN RABBITS.

General Introduction.

The present investigation was undertaken from November, 1902, to July, 1904, with the object of clearing up some doubtful points in uterine and ovarian physiology in rabbits. It may be conveniently divided into four divisions. The experiments were performed by Sir Victor Horsley, to whose kind assistance I am much indebted.

1. To investigate the effect of the removal of the uterine cornu on the ovary of the same side, and also the effect of removal of the whole uterus on ovarian growth and function.

2. To inquire into the nature of, and the conditions governing the secretion of a peculiar saline fluid by the endometrium and mucous membrane of the Fallopian tubes, and to ascertain what influence this secretion exercises when retained under pressure and absorbed into the circulation, on oestrus, ovulation, pregnancy, and the formation of lutein tissue or corpora lutea in the rabbit.

3. To ascertain whether any compensatory hypertrophy takes place in the remaining ovary in the rabbit after removal of one ovary, and if so, under what conditions it occurs.

4. To ascertain by experiment some of the conditions under which abdominal pregnancy and abdominal abortion occur in the rabbit.

Part I.

Much work has been done by physiologists—Fraenkel, Heape, Marshall and Jolly, etc.—and by surgeons—Spencer Wells, Tait, and others—and much is now known about the influence of the ovaries on uterine function, but few facts have been recorded as to the influence of the uterus and Fallopian tubes on the ovaries and on ovarian function. The first point was to determine what effect removal of the whole uterus or one half of the organ in the rabbit exercised on the occurrence of oestrus, ovulation, and pregnancy.

Experiment I (Rabbit 2).

The whole uterus, including the cervix uteri but excluding the Fallopian tubes, was removed on November 20th, 1902. Oestrus and coitus occurred at monthly intervals on February 15th, March 12th, and April 11th, 1903. The animal was killed on April 13th, 1903, forty-eight hours after the last coitus.

DESCRIPTION OF ILLUSTRATIONS.

Fig. 1, Plate 1.—Rabbit 2, Experiment I. Ovaries after hysterectomy. A, Left ovary; B, right ovary showing recently-ruptured follicles.

Fig. 2, Plate 3.—Rabbit 2, Experiment I. Ovaries after hysterectomy; section of left ovary (× 180 diameters). Shows retrograde changes in follicles A and B.

Fig. 3, Plate 3.—Rabbit 2, Experiment I. Section of right ovary (× 180 diameters). Shows pseudo-corpus luteum at A, maturing follicles at B.

Fig. 5, Plate 1.—Rabbit 1, Experiment II. Ovaries after removal of the uterine cornu and subsequent pregnancy. A, Right ovary; B, left ovary; both equal in size and both contain numerous corpora lutea, C.

Fig. 6, Plate 1.—Rabbit 6, Experiment III. Ligature of one uterine cornu; uterus and appendages removed and vagina laid open A, Ligatured portion of right cornu distended with fluid. Hydrometra. B, Left uterine cornu; C, left ovary showing haemorrhagic follicles.

Fig. 32, Plate 1.—Rabbit 13. Restoration of canal after ligature of uterine cornu. A, Right uterine cornu laid open; B, catgut ligatures partly free in mucous canal; C, right Fallopian tube adherent and distended with clear fluid hydrosalpinx.

Fig. 7, Plate 1.—Rabbit 31, Experiment V. Uterus and appendages after transplantation of one uterine cornu. A A, Portions of right uterine cornu transplanted and distended with clear fluid. Hydrometra C, Left uterine cornu containing two fetuses; B, right ovary.

Fig. 8, Plate 1.—Rabbit 31, Experiment V. Shows the left uterine cornu and vagina laid open. A, Vagina and left os uteri; B B, hydrometric transplanted cornu; C C, two placental attachments; D D, adenomatous polypi.

Fig 10, Plate 1.—Rabbit 9, Experiment VI. Uterus and vagina three months after complete oöphorectomy. A, Ligatured and distended portion of right uterine cornu; B, vagina laid open. Bristles inserted in each os uteri.

Fig. 11, Plate 3.—Rabbit 9, Experiment VI. Transverse section of distended right uterine cornu (× 30 diameters). Shows atrophy of uterine wall and endometrium.

Fig. 14, Plate 1.—Rabbit 14, Experiment XII. Effect of ligature of uterine cornu. C, Left or ligatured cornu laid open; A, adenomatous sessile polypus; B, villous polypus.

Fig. 15, Plate 3.—Rabbit 14, Experiment XII Transverse section of polypus and uterine wall at A (× 180 diameters).

Fig. 16, Plate 1.—Rabbit 14, Experiment XII. A, Cystic right ovary.

Fig. 17, Plate 3.—Rabbit 14, Experiment XII. Section of right ovary (× 30 diameters), showing cyst.

Fig. 18, Plate 1.—Rabbit 12, Experiment XIII. Uterus and appendages after transplantation of right ovary A, Left uterine cornu, containing eleven fetuses; B, right uterine cornu, empty; C, transplanted atrophic right ovary, adherent to uterine cornu; D, left ovary, containing eleven corpora lutea; E, vagina.

Fig. 19, Plate 2.—Rabbit 17, Experiment XIV. Uterus and appendages after transplantation of right ovary. A, Left uterine cornu, containing four fetuses; C, right ovary, adherent to posterior surface of uterus; D, right uterine cornu, empty; E, left ovary; B, right Fallopian tube hydrosalpinx.

Fig. 20, Plate 2.—Rabbit 17, Experiment XIV. A, Right transplanted ovary; B, left ovary.

Fig. 22, Plate 3.—Rabbit 17, Experiment 14. Portion of right ovary (× 60 diameters). Shows, A, corpus luteum of pregnancy undergoing retrograde changes.

Fig. 21, Plate 3.—Rabbit 17, Experiment XIV. Section of left ovary (× 60 diameters.) X X, Corpora lutea.

Fig. 27 Plate 2.—Rabbit 3, Experiment XV. Compensatory hypertrophy in left ovary after removal of right ovary and hysterectomy two and a half months earlier. A, Left ovary; B, right ovary.

Fig. 28, Plate 2.—Rabbit 3, Experiment XV. A, Left ovary attached to subperitoneal fat; B, pseudo-corpora lutea; C, vesicular follicles; D, Fallopian tube.

Fig. 29, Plate 4.—Rabbit 3, Experiment XV. Section of left hypertrophied ovary (× 60 diameters). Shows overgrowth of stroma, B, and pseudo-corpus luteum, A.

Fig. 30, Plate 4.—Rabbit 3, Experiment XV. Section of right ovary (× 60 diameters) removed at operation. A A, Follicles containing ova.

Fig. 31, Plate 2.—Rabbit 24, Experiment XV. Compensatory hypertrophy in left ovary after unilateral oöphorectomy. A, Left ovary, weight, 15½ gr.; B, right ovary, weight 8 gr. Both contain corpora lutea.

Fig. 33, Plate 2.—Rabbit 13, Experiment XVII. Compensatory hypertrophy after unilateral oöphorectomy. B, Left ovary double the weight of A, right ovary removed two and a half months before; X, corpora lutea.

Fig. 34, Plate 4.—Rabbit 13, Experiment XVII. Section of left ovary (× 60 diameters). Shows pseudo-corpora lutea.

Fig. 35, Plate 4.—Rabbit 13, Experiment XVII. Section of right ovary (× 60 diameters).

Fig. 13, Plate 2.—Rabbit 8, Experiment XIX. Compensatory hypertrophy after unilateral oöphorectomy. A, Hypertrophied left ovary; B, right ovary.

Fig 36, Plate 1.—Rabbit 19, Experiment XX. Absence of compensatory hypertrophy after unilateral oöphorectomy. Coitus and pregnancy prevented. A, Left ovary; B, right ovary.

Fig. 37, Plate 1.—Rabbit 25, Experiment XXI. Absence of compensatory hypertrophy after unilateral oöphorectomy. No coitus. A, Left ovary; B, right ovary.

Fig. 38, Plate 1.—Rabbit 23, Experiment XXIII. Absence of compensatory hypertrophy after unilateral oöphorectomy and hysterectomy three months earlier. A, Left ovary removed at operation; B, right ovary removed at *necropsy*.

Fig. 41, Plate 2.—Rabbit 15. Effect of coitus on rupture of follicles. A, Left ovary twenty-four hours after coitus (shows numerous raised ruptured follicles); B, right ovary removed during pregnancy one month before.

Fig. 46, Plate 2.—Rabbit 27, Experiment XXVII. Uterus and vagina after formation of vaginal fistula and closure of upper uterine end. A A, Uterine cornua distended with creamy fluid; B, distended vaginal *cul de sac*.

Fig. 47, Plate 2.—Rabbit 27, Experiment XXVII. A, Right ovary; B, left ovary. Both show hypertrophic changes with pseudo-corpora lutea, X.

Fig. 48, Plate 2. Rabbit 11, Experiment XXVIII. Peritoneal abortion after formation of utero-peritoneal fistula. Abdomen laid open. Intestines removed. A, Fetus enclosed in membranes lying free in peritoneal cavity; X, site of utero-peritoneal fistula; B, left ovary.

Fig. 49, Plate 2.—Rabbit 11, Experiment XXVIII. Mummified fetus and placenta, A, with membranes removed.

Fig. 50, Plate 2.—Rabbit 11, Experiment XXVIII. Uterus and appendages. B, Uterine cornua laid open below the fistula; C, utero-peritoneal fistula with everted mucous membrane; A A, position of fetus in right and left uterine cornu above the fistula.

Fig. 51, Plate 4.—Hypertrophy of ligatured cornu during pregnancy. No hydrometra. Transverse section of ligatured cornu (× 30 diameters).

Fig. 51A, Plate 4.—Hypertrophy of ligatured cornu during pregnancy. No hydrometra. Transverse section of ligatured cornu (× 20 diameters).

Both ovaries (Fig. 1) are normal in appearance; each contains several red, raised, and recently-ruptured follicles, together with several dull-yellow, slightly-raised spots, the corpora lutea of the follicles of the previous ovulation.

Microscopic section (Fig. 2) shows two of these latter corpora lutea in the left ovary, Fig 3 two of the mature or unruptured follicles in the right ovary.

This experiment shows that panhysterectomy has no deterrent effect on ovulation, and that it does not prevent the occurrence of oestrus and ovulation at periodically-recurring intervals.

Experiment II (Rabbit 1).

Removal of one uterine cornu has no detrimental effect on the corresponding ovary on the same side.

The left uterine cornu was removed on November 20th, 1902, the vaginal portion, os, and cervix, being left. Oestrus and coitus occurred on February 12th, 1903; this was followed by abortion. Coitus again occurred on March 12th, 1903, and a litter of six young was born on April 12th.

The animal was killed on April 15th, 1903.

The left os uteri is hypertrophied and has undergone, equally with the right os, the changes incidental to pregnancy.

The left ovary (Fig 5) is equal in size to the right ovary, and contains the remains of five corpora lutea of pregnancy, the right ovary containing six.

This experiment illustrates the fact, which I have repeatedly verified, that the number of corpora lutea in one ovary generally corresponds with the number of fetuses in the uterine cornu of the same side, and means, of course, that under normal conditions all the ova which escape from the ovary at any one oestrus and ovulation become fertilized and effect a lodgement in the uterus. Further, only those follicles which have ruptured and shed ova at the time pass on into the stage of corpora lutea of pregnancy.

Further, the experiment also demonstrates the important fact that the occurrence of pregnancy, or the imbedding of fertilized ova in one uterine cornu exercises an equal influence or stimulus on both ovaries, and not only on the ovary corresponding to the pregnant cornu, thus strongly suggesting the inference that it is not by way of the nervous system, but by means of some secretion or substance circulating in the blood, that the stimulus is conveyed to the ovary.

In fact, the bicorned or double uterus (in the rabbit) acts, as far as the function of pregnancy or providing a nidus for the growth of fertilized ova is concerned, as one organ or gland; just in the same way that the two ovaries functionate as one gland as far as the functions of ovulation and the production of an internal secretion are concerned.

Part II.

In the course of some experiments on the production of hydrometra and hydrosalpinx in the rabbit and guinea-pig carried out in 1899,[1] I showed that the normal secretion of the endometrium and the mucous membrane of the Fallopian tubes in the rabbit and guinea-pig and the Fallopian tube in the case of the sheep is a clear watery saline fluid having a low specific gravity of 1010 to 1012 and containing a large quantity of chloride of sodium in solution with a trace of calcium phosphate. It also contains serum albumin but no globulin and a small quantity of an albumose. It is now recognized that the watery fluid which collects under pressure in the occluded Fallopian tube in the human subject is the secretion of the mucous membrane lining the tube and not an inflammatory product.

The object of the following experiment was to ascertain the conditions under which this secretion occurs in the rabbit:

Experiment III (Rabbit 6).

The right uterine cornu was doubly ligatured with silk on December 20th, 1902. Oestrus and coitus occurred on February 23th, 1903, and again on March 12th, 1903; this was followed by pregnancy, the animal was killed on May 7th, two months later.

Fig. 6 shows the distension by saline fluid (hydrometra) of the upper portion of the right cornu after double ligature. The occurrrence of this distension following pregnancy will be referred to later, and it may here be explained that in cases of double ligature of a portion of uterine cornu in the rabbit, and in which at the necropsy some weeks later no hydrometra has been found, the explanation has been that the ligature material (and this applies especially to catgut) has made its way into the cavity of the tube or cornu, and in this way the continuity of the mucous canal has been restored and the fluid allowed to escape.

This is well shown in Fig. 32 (Rabbit 13) in which the tube was found empty and the catgut ligatures projecting free into the mucous canal.

Thus is experimentally produced the condition which arises in those cases in the human subject where pregnancy has occurred after ligature of the Fallopian tube or tubes. This secretion by the endometrium of the uterine cornu and Fallopian tube takes place independently of nervous influence, and occurs in ligatured portions of cornu that have been transplanted to distant parts of the abdominal cavity, and the same thing occurs in transplanted tubes. This point will be referred to later.

Experiment IV (Rabbit 30).

Two portions of the right uterine cornu were transplanted and grafted on the peritoneum of the abdominal wall on March 1st, 1904.

A cystic swelling the size of a walnut could be felt a fortnight later at the site of the transplanted cornu, through the abdominal wall. This swelling subsequently subsided after pregnancy occurred in the normal cornu. The animal was killed on July 30th, and the transplanted portion of the uterus had undergone atrophy.

Experiment V (Rabbit 31).

Two portions of the right uterine cornu were excised and transplanted to the peritoneum of the abdominal wall on March 1st, 1904. An abdominal swelling formed as in the last case. The animal became pregnant on May 12th (the swelling being still present), and was killed on May 21st, 1904.

Fig. 7 shows the two portions of transplanted cornu, cystic and distended with saline fluid, and the pregnancy in the left cornu.

Fig. 8 shows the left uterine cornu laid open, exposing the sites of the two placental attachments, and a number of adenomatous polypi, to which reference will be made later.

This uterine secretion occurs after complete removal of both ovaries and in the absence of oestrus or coitus, thus:

Experiment VI (Rabbit 9).

Both ovaries were completely removed on February 14th, 1903. The right uterine cornu was doubly ligatured. The effect of double oöphorectomy in this rabbit was, as usual, to abolish all sexual appetite; in other respects the animal was in good health and fat. It was killed on May 7th, 1903, nearly three months after the operation. The mammary glands had practically disappeared, and the teats were smaller than in the normal rabbit in the non-pregnant condition. The whole uterus and vagina had undergone a very marked degree of atrophy, the walls of both were thin and fibrous, not thick and muscular. Both os uteri were small and shrunken. No trace could be found of either ovary.

Fig. 10 shows the uterus and vagina removed, the left uterine cornu is a small thin tube, and the vagina thin, fibrous, and atrophic.

The right uterine cornu between the ligatures has its thin, atrophied, almost translucent walls distended with the clear watery fluid described above, hydrometra being present.

The vagina is laid open, and bristles are inserted into the two minute canals of the os uteri.

Fig. 11 shows a cross section of a portion of the distended cornu and the atrophy of the villi of the endometrium.

Absence of Saline Secretion during Pregnancy.

This saline secretion of the uterine cornu, while occurring under all other conditions, and becoming manifest on occlusion of the uterine canal, practically ceases, or is at any rate greatly diminished in amount, during pregnancy.

Experiment VII (Rabbit 16).

A fistulous opening was established by stitching the incised and everted mucous wall of the right uterine cornu to the skin in the abdominal incision, the opening of this fistula when repeatedly examined was always found moist and bathed with a muco-watery fluid. This continued for five weeks, when the animal was killed.

Experiment VIII (Rabbit 21).

A uterine fistula was established in this as in the last experiment on July 2nd, 1903. The animal became pregnant on August 1st, and was killed on August 7th, 1903. After the occurrence of pregnancy, and for some days before the animal was killed, the uterine fistula had dried up, and the everted mucous membrane had become drawn in. Both ovaries contained small corpora lutea of early pregnancy.

The hypertrophy of the ligatured uterine cornu and the absence of distension by saline secretion during the presence of pregnancy in the other cornu are well shown in Figs 51 and 51A.

Experiment XIX.

Right uterine cornu ligatured at vaginal and Fallopian ends two days after coitus.

The animal was killed fourteen days later. The right cornu was not distended; it contained a little milky secretion, and its walls were thick and spongy.

The left cornu contained five fetuses.

These experiments show that if the uterine cornu be ligatured after impregnation has occurred, no saline secretion occurs, and no distension of the occluded tube by hydrometric fluid.

The same absence of saline uterine secretion was observed in the uterine fistula in Rabbit 21, after the occurrence of pregnancy, while continuously present in Rabbit 16, in which pregnancy did not occur.

The apparent exceptions in which ligatured portions of uterine cornu have been found distended by saline fluid at the necropsy (pregnancy being also present) are probably due to the fact that the collection of secretion occurred before the occurrence of pregnancy and remained during its continuance.

We have seen that this secretion occurs independently of any ovarian influence, and that it is present in transplanted portions of cornu in which all nervous influence has been severed.

An extended inquiry into this function of the oviduct in animals below the mammalia would probably yield valuable information as to the steps by which the function of the endometrium in the higher vertebrates has been evolved.

It is, at any rate, a suggestive fact that in the human female, while the lower or uterine portion of the oviduct has undergone special changes, the secretion of the upper portion or Fallopian tube still remains a saline watery fluid like that of the whole duct (uterus and Fallopian tube) in the lower mammals.

It is certain that this secretion of the endometrium must bear some reference to the nutrition, while in the duct, of the ova shed by the ovary, and it is impossible not to be struck by the marked saline character of this watery fluid and its resemblance to sea water, as far as chemical constitution is concerned.* Is it possible that we have here in this fact a relic of the earlier stages of vertebrate evolution, in which, as in the aquatic species, the ova were shed into sea water?

One other point about this saline secretion still remains, and that an important one. Under ordinary conditions of patency of the canal no collection of secretion occurs, no distension of the tube by fluid under pressure, and any fluid that is secreted by the endometrium is either resorbed or flows into the vagina.

Under the altered conditions of a ligatured cornu the fluid is retained under a certain degree of pressure, and the question arises as to what influence this retained secretion exercises on the uterus, on the ovaries, and on the animal itself?

Influence of this Uterine Secretion on the Uterus.

In nearly all cases of double ligature of one uterine cornu and retention of saline secretion, some interference has occurred with the normal sequence of oestrus, coitus, impregnation, and the imbedding of the fertilized ova on the endometrium of the healthy cornu.

(*a*) Sexual appetite is not abolished; on the contrary, the oestral period is prolonged, and occurs more frequently than is natural. Thus, in Rabbit 30, in which a transplanted portion of the uterine cornu had become hydrometric, repeated coitus occurred every few days from March 16th (two weeks after operation) till May 20th, and pregnancy only occurred at this latter date, and after atrophy of the transplanted portions of the cornu had become complete. The same frequency of coitus and absence of pregnancy occurred also in Rabbit 31.

(*b*) Interference with the normal imbedding of fertilized ova in the endometrium occurs, or if the ova have become imbedded, there is a great tendency for abortion to occur—that is, there is some interfering influence exercised by the retained fluid on the normal relationship between trophoblast and endometrium. Thus:

Experiment XI (Rabbit 31).

After transplantation of the right uterine cornu only two fertilized ova succeeded in establishing themselves in the lower portion of the left or healthy cornu. (Fig. 7.) On opening the cornu, the mucous membrane of the tube above the fetal sac was found covered with numerous sessile, mucous polypi (see Fig. 8), which on microscopic section were found to be adenomata. (See Fig. 15.)

These adenomatous polypi are, I believe, the sites of the imbedding of abortive ova, or abortive placental attachments. This is rendered likely from the fact that the lower and larger of the polypoid masses resembles a placental site after an early abortion, and has a central umbilicated necrotic area, and contains syncytial cells.

Experiment XII (Rabbit 14).

That the association of retained secretion and a polypoid or adenomatous condition of the endometrium is not an accidental one is rendered probable by this experiment, in which the left extreme cornu was doubly ligatured on June 3rd, 1903. Repeated oestrus occurred, but no coitus was allowed, and when the animal was killed on July 5th, 1903, the left or ligatured cornu was found understended, because the ligatures had already cut their way through the mucous membrane, and the patency of the canal was restored.

The upper portion of the tube, however, contained two polypi, one villous and pedunculated, one sessile and adenomatus. Fig. 14 shows the polypi in position, and Fig. 15 the microscopical appearance of a section of the lower growth under a low power.

In this case also the right or remaining ovary was cystic (Fig. 16 and Fig. 17), the only occasion on which I have detected a pathological cyst in a rabbit's ovary. The left ovary was removed at the operation.

The Influence of this Uterine Secretion on the Ovaries.

(*c*) It was thought that some light might be thrown on the question of uterine influence on ovarian function by experimental interference with the conditions under which this uterine saline secretion is produced.

It is, of course, well known that the presence of a fertilized ovum, or ova imbedded in the endometrium, the presence in fact of a living trophoblast, is necessary to ensure the active growth of lutein tissue in the ruptured follicles in the ovaries, and that these corpora lutea are necessary for the continued nutrition of the trophoblast within the uterus until the placenta has formed. (See Fraenkel, Marshall and Jolly, and others.)

The question arises as to the manner in which this stimulus is conveyed to the ovary. It is by blood stream or by nerve impulse? By what means, in fact, does the ovary become aware, so to speak, of the occurrence of pregnancy?

That some reaction between endometrium and trophoblast is necessary for the stimulus to occur is rendered probable by the fact that in cases of pregnancy occurring outside the uterus, either abdominally or in the broad ligament in the human subject, the corresponding corpora lutea are ill developed, while for the purpose of this reaction the cavity of the Fallopian tube and uterus may be regarded as one membrane.

It is quite possible that a substance may be elaborated at the site of this reaction between trophoblast and uterine epithelium, which, circulating in the blood, exercises this stimulating influence on the lutein cells of the ovary.

And further, it is probable that this hypothetical substance, and some constituent in the saline uterine secretion, are mutually antagonistic as far as their effect on the lutein cells of the ovary is concerned.

An attempt was made to throw light on this question of the transference of the ovarian stimulus (by circulation or nerve influence) by transplanting one ovary and then observing the effect on the corpora lutea in the transplanted ovary at a subsequent pregnancy. Unfortunately it frequently happens that atrophic changes occur in the transplanted ovary, which abolish or render doubtful any subsequent effects of pregnancy.

Experiment XIII (Rabbit 12).

The right ovary with the mesovarium was entirely detached and transplanted to the parietal peritoneum in the right flank, May 25th, 1903. Primary aseptic healing occurred. The animal became pregnant on June 19th producing nine young.

Pregnancy again occurred on July 27th, and the animal was killed on August 7th. The left uterine cornu contained eleven fetuses (Fig. 18), and the left ovary eleven corpora lutea. The right or transplanted ovary could be recognized with difficulty, and had undergone atrophic degenerative changes, and no corpora lutea could be detected.

Experiment XIV (Rabbit 17).

The right ovary was transplanted to the peritoneum over the right psoas muscle in two stages. In the first stage on June 13th, 1903, the ovary was freed from all attachments to surrounding parts, except its attachment to the Fallopian tube; the ovary, however, broke away from this anchorage and

* A quantitative chemical analysis of hydrosalpinx fluid from the human subject gives 10.12 parts per 1,000 of sodium chloride. The proportion in blood plasma and serous fluids being 6 or 7 parts per 1,000. Sea water has a specific gravity of about 1,022 and contains 25 parts per 1,000 of sodium chloride.

became adherent to the back of the uterus near the vagina. Seven days later the abdomen was reopened and the Fallopian tube attachment ligatured and divided. Aseptic healing occurred. The animal became pregnant on July 4th, and was killed on July 19th.

The left uterine cornu contained four fetuses (Fig. 19) and the left ovary six corpora lutea. The right or transplanted Fallopian tube was slightly distended (hydrosalpinx). Fig. 20 shows the two ovaries side by side. The right or transplanted ovary was rough on the surface from adhesions; it showed signs of degenerative changes but was not markedly small. It had some raised eminences on its surface, and Fig. 22 shows the appearance at one of these sites under a low power; the appearance is that of a somewhat modified and degenerate corpus luteum of pregnancy—an area of epithelial cells surrounded by a vascular ingrowth from surrounding tissue.

Fig. 21 shows a section of the left ovary. Thus in this case a somewhat aberrant corpus luteum had occurred during the early stage of pregnancy in a transplanted ovary in which all original nervous connexions with the uterus had been severed, thus lending support to the supposition that it is by means of the circulatory system, by means of some substance circulating in the blood, that the stimulus is conveyed from the uterus to the ovary which provokes the growth of lutein cells.

One other apparent effect of the retention under pressure of uterine secretion on the ovaries must be mentioned. In several cases after ligature and operations on the uterus the follicles in the ovary on the healthy side have been dark red or black in colour, due no doubt to haemorrhage. This is shown in Fig. 6 (Rabbit 6), in which the hydrometric right cornu is associated with black haemorrhagic follicles in the right ovary.

Influence on Health and Nutrition.

The retention or absorption of this saline fluid besides its effect on the ovaries and the imbedding of fertilized ova has some prejudicial effect on the health and nutrition of the animal.

Experiment XIV (Rabbit 22).

A utero-peritoneal fistula was established at the upper end of both uterine cornua by longitudinal incision, and stitching back the everted mucous membranes at the margins of the incision.

The animal, though well nourished, seemed in bad health, dull, with staring coat; coitus occurred and probably failure of fertilized ova to become imbedded. The two ovaries contained two crops of follicles, a number of corpora lutea and a crop of red, raised mature follicles; the animal in fact presented the symptoms of some toxaemia probably associated with the abortive impregnation.

PART III.

Compensatory Hypertrophy in Ovary.

There are but few recorded physiological observations bearing on the question of the occurrence of compensatory hypertrophy in ductless glands.

On the other hand, in the case of glands having a definite external secretion or excretion hypertrophy under certain conditions is well-recognized. Thus, in the case of the urinary organs, if one kidney be removed the remaining organ, after a certain lapse of time, increases in size and responds to the call made upon it by the organism for increased excretory effort.

For the purpose of the present inquiry we may regard the ovaries as ductless glands, for in addition to the special function of ovulation (the excretion or shedding of ova) it has been now established that the ovaries are responsible for the manufacture of a substance or substances which, when thrown into the lymph or blood stream, acts on the organism as an internal secretion.

The first point to determine was whether, after removal of one ovary, any increased growth or hypertrophy occurred in the remaining organ.

Experiment XV. (Rabbit 3).

The whole uterus, together with the right ovary and tube, was removed on December 24th, 1902, the left ovary and Fallopian tube being left. Primary healing and rapid recovery of health occurred.

Repeated coitus took place during February, 1903, and the animal was killed on March 9th, 1903. On opening the abdomen after removal of the intestines there was no peritonitis, and the utero-vaginal stump was soundly healed. The left ovary was much larger than the right when removed two months and a half earlier (see Fig. 27), in fact more than twice as large; the surface was irregular and studded with numerous raised projections like partially-developed corpora lutea of pregnancy. There were also a number of clear vesicular mature follicles; this condition is well seen in Fig. 28, which is an enlarged view of the ovary resting on the fat covering the psoas muscles, with the end of the Fallopian tube on the left side.

Micro-sections of both ovaries also exhibit striking differences (Fig. 30). The right ovary, removed earlier, is full of maturing follicles containing ova, while a section from the corresponding pole of the left ovary shows very few follicles but a large increase in the ovarian stroma structures, and gives an appearance resembling that seen in sections of ovaries containing corpora lutea during pregnancy (Fig. 29).

Thus in this experiment marked compensatory hypertrophy occurred in the left ovary after the removal of the right ovary two and a half months earlier. It is, however, very important, as we shall see later, to bear in mind that repeated coitus had occurred in the interval, the associated hysterectoromy, although important, and probably accessory to, is not necessary to, the occurrence of hypertrophy of the ovary.

Experiment XVI (Rabbit 24).

The right ovary was removed at mid-pregnancy on July 18th, 1903. It weighed, after hardening in formalin, 8 gr., and contained eight corpora lutea. Abortion occurred after the operation. Coitus took place on August 11th; pregnancy following, and a litter of seven young rabbits was born on September 12th, of which three were reared. The animal became pregnant again on November 29th, and was killed during pregnancy on December 20th.

The left ovary was found to have undergone a marked increase in size—it weighed after hardening 15½ gr., and contained seven corpora lutea.

These were not individually quite so large as the corpora lutea found in the right ovary on removal of a slightly earlier date of pregnancy, so that the increase in size of the left ovary is due to hypertrophy of ovarian stroma tissue, and not wholly to increase of lutein tissue. (See Fig. 31.)

In this experiment also the removal of the right ovary was followed after an interval of five months (during which time pregnancy had occurred on two occasions) by a marked compensatory hypertrophy of the remaining or left ovary.

Experiment XVII (Rabbit 13).

The right ovary was removed and a portion of the right uterine cornu ligatured during pregnancy on May 21st, 1903. Abortion followed the operation on June 8th. The animal became pregnant again on June 14th, and was killed during pregnancy on July 4th.

The left ovary was found to have undergone a marked hypertrophy, and weighed after hardening double the weight of the right ovary, when removed two and a half months earlier. It contained nine corpora lutea of pregnancy. Fig. 33 shows the two ovaries for comparison.

Fig. 34 and Fig. 35 are photomicrographs under low power of sections of the left and right ovaries respectively, and show the characteristic appearance of increase of stroma and lutein tissue in the hypertrophied or left ovary.

It is important also to observe that in this experiment the left uterine cornu contained eight fetuses or placental sites, while the corresponding left ovary contained nine corpora lutea. Now, since the right uterine cornu was of course empty, the presence of a litter of eight or nine young illustrates the fact that besides structural changes, a marked increase of physiological activity in the shape of increased ovulation had occurred to make up for the deficiency due to the removal of the right ovary.

This phenomenon was more strikingly shown in the next experiment.

Experiment XVIII (Rabbit 12).

The right ovary was transplanted on May 21st, 1903, but as almost complete degeneration and atrophy occurred, it may be regarded for the purpose of the present experiment as having been removed. The animal became pregnant for the first time on June 19th and produced a litter of nine young. It became pregnant for the second time on July 27th, and was killed during pregnancy on August 7th.

Fig 18.—*Post mortem* the left uterine cornu was found to contain eleven living fetal rabbits, the right cornu being of course empty. The left ovary was markedly hypertrophied and contained eleven corpora lutea of early pregnancy.

Thus in this case the left or only active ovary had produced two crops of ova, subsequently fertilized, one of 9 and one of 11 in two and a half months, both of which collections of fetuses were nourished in one uterine cornu. Assuming that the right ovary had also been equally functionally active in this rabbit, we should have had two litters, one of 18 and one of 22 young rabbits in two and a half months—a very unusual occurrence—a fact which serves to emphasize the heightened physiological activity occurring in the remaining ovary.

The next experiment illustrates the effect of unilateral oöphorectomy under rather different conditions.

Experiment XIX (Rabbit 8).

The right ovary was removed and the right uterine cornu ligatured on February 14th, 1903, in the non-pregnant condition. Pregnancy occurred on March 25th, and two young were born dead on April 28th. The animal was killed six days later. Fig. 13 shows the two ovaries side by side for comparison, the left being double the size of the right.

In all these five experiments, repeated coitus had occurred after the removal of the one ovary, and with the exception of Experiment XV pregnancy once, or repeated had occurred in each case; that this association is important and that coitus, or pregnancy, or both are important stimuli in connexion with the compensatory hypertrophy which occurred in the remaining ovary in these cases is shown by the fact, that when after removal of one ovary coitus and consequently pregnancy are prevented, little or no compensatory hypertrophy occurs, thus:

Experiment XX (Rabbit 19).

The right ovary was removed in a three-parts grown rabbit on July 2nd, 1903. No coitus occurred; the rabbit was killed on October 21st, 1903, three and a half months later. Fig. 36 shows the two ovaries. No hypertrophy has occurred in the left ovary; in fact, it is smaller than the right when removed three and a half months before.

Experiment XXI (Rabbit 25).

The right ovary was removed on July 25th, 1903. No coitus was allowed. The animal was killed on October 22nd. No compensatory hypertrophy was found in the left ovary. Fig. 37 shows the two ovaries, which are equal in weight.

Experiment XXII (Rabbit 18).

The right ovary was removed during pregnancy on June 15th, 1903. Abortion occurred. The animal was killed on July 8th, 1903. No compensatory hypertrophy had occurred in the left ovary, which is smaller than the right when the usual proportion between the ovary of the non-pregnant and that of the pregnant condition is considered. The interval of time, however, in this case after operation was less than one month.

The next experiment can be usefully compared with Experiment XV (Rabbit 3).

Experiment XXIII (Rabbit 23).

The whole uterus was removed, together with the left ovary, during early pregnancy, on July 18th, 1903. No coitus was permitted, and the animal was killed on October 21st, 1903. *Post mortem*, the body was well nourished; the right ovary was considerably smaller than the left, even when allowance was made for the corpora lutea present in the latter (see Fig. 38)

Thus, in these four last experiments no coitus, and consequently no pregnancy, occurred after the removal of the one ovary, and when the animals were killed, at periods from one month to three months after the operation, no compensatory hypertrophy was discovered in the remaining ovary. Moreover, in the last experiment (Experiment XXIII, Rabbit 23) the uterus was also removed, as in Experiment XV (Rabbit 5), in which case marked compensatory growth occurred in the remaining ovary, the difference being, however, that frequent coitus occurred in Experiment XV, while in the last experiment (Experiment XXIII, Rabbit 23) it was not permitted.

The consideration of these facts strongly supports the conclusion that the occurrence of sexual intercourse, or pregnancy, or both, are in the case of the rabbit powerful stimuli of ovarian growth and function, and cause compensatory hypertrophy to take place in an ovary after removal of the corresponding organ or half the sum total of ovarian gland substance some time previously.

I have been very careful to apply this statement to the case of the rabbit only. In the human female, in several cases in my own personal experience, in which, after removal of one ovary and tube some years earlier, it became necessary to remove the remaining ovary, no striking increase in size was noticeable. Further observations are necessary on this point, and also on the question of the occurrence of compensatory hypertrophy after unilateral oöphorectomy in other animals besides rabbits under varying conditions.

Coitus and Ovulation.

There is, however, one point of importance in this connexion. It has been shown by W. H. Heape (1897) that whatever may be the relationship between oestrus and ovulation in many animals, in the rabbit, at all events, it is the stimulus of coitus occurring during oestrus, and the presence of spermatozoa in the uterus which actually determines and provokes the rupture of the mature follicles and brings about the shedding of the ova.

My own observations confirm this, as far as the act of copulation is concerned. If a rabbit be killed from twenty-four to forty-eight hours after the occurrence of coitus during oestrus and the ovaries be carefully examined, fully mature, red, raised follicles will be found studding the surface of the glands with the umbilicated surface characteristic of recent rupture, and in many cases little portions of blood clot or fibrin are found adhering to the ruptured surfaces.

Experiment XXIIIa (Rabbit 15).

Fig. 41 shows the ovaries of a rabbit killed twenty-four hours after coitus, the left ovary containing eight just-ruptured mature follicles. The right ovary had been removed by operation during pregnancy one month earlier.

Experiment XXIIIb (Rabbit 16).

Shows the same relationship between coitus and follicular dehiscence. (See also Fig. 1, Experiment I.)

The next point to determine was the actual factor in the act of coitus responsible for this stimulating effect on the ovary. Was it the nervous stimulus of copulation ending in increased vascular turgescence of the ovarian vessels, or the presence of semen in the genital canal of the female rabbit which caused the result?

To determine this point artificial insemination was carried out as follows:

Experiment XXIV (Rabbit 29).

After ascertaining that the animal was in the condition of oestrus, semen from the vagina of another rabbit just impregnated was injected into the vagina of Rabbit 29 on March 15th, 1904. An inspection of the right ovary twenty-four hours later showed four maturing, but unruptured, follicles. Natural coitus occurred four days later, and when killed twenty-four hours afterwards the follicles were ruptured.

Thus insemination without coitus is not as effectual as an ovarian stimulus as coitus and insemination. (See also Experiment XXVI, Rabbit 27.)

On the other hand, coitus without insemination is not so effective in causing dehiscence as coitus with insemination.

Experiment XXV (Rabbit 28)

A vaginal *cul-de-sac* was formed on March 1st, 1905, by dividing the vagina across within the abdomen, and closing the lower or vaginal end, and returning it into the abdomen, and fixing the upper or uterine end to the skin on the surface of the abdomen. Oestrus and repeated coitus occurred at regular intervals, and the animal was killed on June 14th, 1904, forty-eight hours after coitus. An examination of the ovaries showed some follicles in various stages of growth, but none quite mature or recently ruptured. In connexion with this experiment also two interesting facts may be mentioned:

(*a*) It was noticed on examination of the two os uteri (which were quite visible on holding open the edges of the vaginal fistula opening on the abdomen) that during oestrus, and immediately after coitus had taken place, or even during the manipulation necessary to expose the os uteri, paroxysmal erectile movements occurred in each cervix uteri at frequent intervals, each cervix elongating everting the mucous membrane of the endometrium at each os, and standing prominently into the vagina, then as the turgescence and muscular action subsided the cervix contracted and the endometrium was drawn in again. Such a condition of the cervix uteri and os, and such movements as these must be powerful agents in drawing, almost pumping, the seminal fluid from the vaginal vault into the uterine cornua, and would seem calculated to ensure the impregnation of the animal after coitus.

(*b*) If during these periods of oestrus and sexual excitement an inspection of the os uteri is made, a thin watery discharge will be noticed exuding from each os uteri, which is probably the saline secretion peculiar to the uterus which I have previously described, mixed with a certain amount of cervical mucus, and it is interesting to note that this has a peculiar odour exactly resembling that of the liquor amnii and sebaceous covering of the human fetus when just born.

One other point remained to be settled: that is, whether seminal fluid itself, apart from the living spermatozoa, exercises any stimulating influence on the ovaries when injected into the genital canal of the female rabbit.

Experiment XXVI (Rabbit 33),

A solution of previously desiccated semen in water was injected into the vagina during oestrus—under the microscope this fluid consisted of epithelial cells and dead spermatozoa—on April 15th, 1904. The rabbit was killed twenty-four hours later. No very mature or dehisced follicles were seen in either ovary.

Thus we are brought back to the facts: that the normal and effective stimulus in the case of the rabbit for effecting terminal maturation and dehiscence of ripe follicles and the shedding of ova during oestrus is the act of coitus, and that in association with this act the presence of seminal fluid and living spermatozoa in the upper portions of the uterine canal may also be an important adjunct.

We also know from Experiment XV (Rabbit 3), Experiment XVI (Rabbit 24), Experiment XVII (Rabbit 13), Experiment XVIII (Rabbit 12), Experiment XIX (Rabbit 8), that after previous removal of one ovary, if coitus, or coitus and pregnancy occur, then after a certain interval of time compensatory hypertrophy of structure and an increased functional activity occurs in the remaining ovary.

Whereas Experiments XX, XXI, XXII, and XXIII illustrate the fact that if after removal of one ovary the stimuli of coitus and pregnancy are absent, then little or no compensatory hypertrophy occurs in the remaining ovary.

Further, the hypertrophic changes in the remaining ovary, brought about by the stimulus of coitus, are similar to those produced by pregnancy, that is to say, changes are produced in ruptured follicles which have all the appearances, to the naked eye, and on microscopical examination of the true corpora lutea associated with pregnancy. This is well shown in Figs. 27, 28, 29, and 30 from Rabbit 3, in which, the uterus having been removed, pregnancy was prevented.

The same production of pseudo-corpora lutea by repeated coitus in the absence of pregnancy is seen in Experiment XXV (Rabbit 28) in which insemination took place into a vaginal *cul de sac*, although in this experiment one ovary had not been removed.

The same changes in the ovaries were produced in:

Experiment XXVII (Rabbit 27).

A vaginal fistula was formed on March 1st, 1904, but in this case, unlike Experiment XXV, the lower or vaginal end of the divided vagina was united to the skin of the abdomen and the uterine or upper end closed. As a result of this occlusion of the vagina just below the opening of the uterine cornua a very remarkable distension of the vagina and uterine cornua occurred. The cornua filled the abdomen and were of the size of a full term pregnancy. On opening them they were full (one pint) of a pale yellow cream-like fluid without odour, alkaline in reaction, and consisting under the microscope of epithelial cells and granular débris in a mucoid fluid. (See Fig. 46.) The ovaries showed very markedly the changes found in compensatory hypertrophy, and those seen in ovaries during early pregnancy containing numerous corpora lutea. (See Fig. 47.) In this case repeated coitus had occurred.

Further, coitus during oestrus has the effect in the rabbit (probably by reason of the production of this lutein cell growth in the ovary) of bringing about a certain physical condition in which the animal appears and acts as though it were pregnant and no doubt, as far as subjective sensations are concerned, goes through the same nerve state, thus in both cases of vaginal fistula (Experiment XXV, Rabbit 28 and Experiment XXVII, Rabbit 27) this occurred.

Experiment XXVIII (Rabbit 27).

In this experiment repeated coitus occurred on March 15th. Oestrus was followed by a quiet interval of one month in which the rabbit refused the approaches of the buck, tore off fur and made a nest, no pregnancy, of course, existing. Although we must not forget the largely distended condition of the uterus which may have given rise to sensations of pregnancy.

Experiment XXV (Rabbit 28).

In this experiment the occurrence of coitus on March 23rd was followed by a quiescent interval of nearly a month, in which the animal refused the approaches of the buck, and at the end of the time made a fur nest; pregnancy being, of course, absent.

On the other hand the absence of coitus is followed by a prolongation and increased frequency of the condition of oestrus.

Thus, from the effects which we have seen to follow from coitus, namely:—

(*a*) The dehiscence of mature ovarian follicles;

(*b*) The formation of pseudo-corpora lutea in the ovaries in the absence of pregnancy;

(*c*) The production of a psychical state associated with pregnancy;

we are strongly led to look upon coitus as the stimulus which causes the hypertrophy and the formation of pseudo-corpora lutea in the absence of pregnancy, in those cases in which, after the removal of one ovary, compensatory hypertrophy has occurred in the remaining organ.

It is very suggestive to find that of two experiments in which one ovary together with the whole uterus was removed by operation, the peculiar changes associated with hypertrophy occurred in the remaining ovary in the animal in which coitus was allowed (Experiment XIV, Rabbit 3), and was absent in Experiment XXIII (Rabbit 23), in which coitus was prevented.

It is interesting to find that the compensatory hypertrophy, the increased ovulation, and more frequent oestrus which occurs in the rabbit after unilateral oöphorectomy resembles the result brought about by flockmasters in the case of ewes by means of increased supply of rich food (see Marshall, *Fertility in Scottish Sheep*, 1905).

PART IV.

The following few remarks refer to the experimental production of abdominal pregnancy in rabbits.

In connexion with this subject attention may be drawn to the extreme rarity of any records of abdominal pregnancy in the animal kingdom apart from the human species.

It was thought that by establishing a fistulous communication between the interior of the uterine cornua and the peritoneum the escape of fertilized ova into the peritoneal cavity might be encouraged and their subsequent vascular attachment and growth on the peritoneum produced.

Experiment XXVIII (Rabbit 11).

On March 20th, 1903, both uterine cornua were laid open for a short distance along their free border near the lower end, and the mucous membrane sewn back to the peritoneal coat with catgut in order to prevent early closure of the incision. Coitus occurred on April 9th, 1903. The animal made a nest and appeared as if approaching labour on May 9th, 1903. No young were, however, born.

Coitus occurred again on May 12th and 13th, and the animal was killed on May 21st. The peritoneum contained some clear fluid, and the mammary glands were enlarged and contained milk. Lying in the right flank and quite free from adhesions was a wasted fetal rabbit, together with the placenta, enclosed in a shrunken amniotic sac. It appeared to be about the period of growth of a full-term pregnancy, and was of a yellowish-reddish-brown colour (see Fig. 48). Fig. 49 shows the fetus and placenta attached with the membranes removed.

Fig 50 shows the uterus removed and the uterine cornua laid open below the fistula; the edges of the fistula in the two cornua have coalesced, so that each communicates with the peritoneal cavity by a common opening with a herniated protrusion of mucous membrane surrounding the fistula above this point; each cornua also contains a fetus of about seven or eight days' growth. The ovaries are large; both contain corpora lutea corresponding with the latter pregnancy.

Thus the sequence of events in this experiment was as follows: The animal became pregnant on April 9th, and went nearly to term when peritoneal abortion occurred, one fetus enclosed in its membrane passing through the fistula into the abdominal cavity, possibly others escaped through the vagina, and may have been eaten by the doe. Coitus occurred again three days later, pregnancy following, and when killed eight days later, a second set of fetal sacs occupied each cornua above the fistula.

This experiment should be called the "experimental production of peritoneal or abdominal abortion" rather than "abdominal pregnancy," and exemplifies the probable manner in which practically all abdominal pregnancies occur, that is, by abortion from the abdominal end of, or escape through a rupture in the wall of, a cornu or tube.

These are facts which suggest the conclusion that it is extremely difficult for the early or naked ovum to live in the peritoneal cavity when deprived of the shelter of either tubal or uterine endometrium, and of the nutritive fluid secreted by that membrane.

It is also interesting to note that the presence of a dead fetus in the abdomen does not act in any way as a living fetus in the uterus does as far as the reciprocal action of pregnant uterus on the ovary is concerned. Oestrus, coitus, and pregnancy occurred during the presence of the fetus in the abdominal cavity, a fresh set of follicles matured, ruptured, and underwent the changes of lutein overgrowth characteristic of early pregnancy.

The drawing of any inference from the facts of this experiment with regard to abdominal pregnancy in the human subject would be inadmissible. We are, perhaps, justified in saying this much: That the reason why primary abdominal pregnancy is so rare, almost unknown, in the human subject as in the lower animals, is that a fertilized ovum finds it almost impossible to live in the peritoneal cavity in the absence of any vascular subperitoneal attachment, and that consequently nearly all cases of abdominal pregnancy are secondary, the ovum being launched into the peritoneal cavity at a later stage of growth.

Imbedding of the fertilized ovum in the mucous membrane of the Fallopian tube must depend on an abnormal or altered relationship between ovum and mucous membrane, but in what the abnormal reaction consists we do not yet know, in spite of much investigation.

General Summary and Conclusions.

1. That the presence of functionally active ovarian tissue is necessary for the uterine function, or that portion of it which is concerned with the preparation by the endometrium of a suitable nidus for the imbedding of fertilized ova.

2. The presence of the uterine or endometrium tissue is not, on the other hand, necessary for the carrying on of ovarian function, either ovulation or the production of the internal secretion associated with oestrus.

3. That one function of the endometrium in the anoestrous state is the secretion of a saline, watery fluid of low specific gravity, containing a large amount of chloride of sodium in solution.

4. That there is some antagonism between this endometric function or saline secretion and that portion of the internal secretion of the ovary which is specially concerned in producing pro-oestrous changes in the endometrium preparatory to the imbedding of fertilized ova. That portion of the internal secretion of the ovary which is, in fact, associated with the growth of corpora lutea.

Thus the saline uterine secretion is associated with katabolic, the ovarian secretion with anabolic, changes.

5. The mechanism by means of which the ovary obtains its stimulus from the stimulated endometrium consequent on the occurrence of pregnancy is a circulatory and not a nervous mechanism.

In all probability some substance is manufactured by endometrium or by trophoblast or by both, which reaches the ovary by way of the blood stream, and is also concerned with the increased activity in the mammary glands.

6. That the bilateral and bicorned uterus in the rabbit may be regarded as one gland as far as that function of the endometrium is concerned, which is associated with the preparation of a suitable nidus for fertilized ova.

7. That the bilateral ovaries may also be regarded as one gland as far as the functions of ovulation and production of internal secretion are concerned.

8. That after removal of one portion or half of this gland, the remaining portion is capable, under certain conditions, of undergoing a process of compensatory hypertrophy.

9. These necessary conditions in the rabbit are (*a*) the presence of the stimulus—namely, copulation—which in this animal normally determines ovulation, or (*b*) the stimulus of pregnancy. Under normal conditions these two stimuli occur together.

10. That these hypertrophic changes in the ovary after unilateral oöphorectomy structurally resemble those changes which normally occur in the ovaries during pregnancy in its early stages.

11. That after unilateral oöphorectomy together with hysterectomy in the rabbit, the hypertrophic stimulus is supplied by repeated copulation.

12. The prevention by previous hysterectomy of the secretion of the saline fluid by the endometrium of the anoestrous uterus favours the overgrowth in the ovary of lutein tissue.

The Bearing of the above Conclusions on Various Theories of the Nature and Cause of Menstruation.

We may first premise that of the many hypotheses put forward to explain the phenomenon of menstruation many are opposed by facts, and only one or two need be considered.

The three fundamental points which seem established are:

1. That the whole pro-oestrous process is of the nature of a preparation for the attachment of an embryo (Marshall and Jolly).

2. In addition to ovulation the mammalian ovary elaborates an internal secretion which at recurring periods is the cause of pro-oestrus and oestrus.

3. The corpora lutea form a ductless gland which is necessary for the nutrition of the trophoblast during the early stages of pregnancy and subsequently atrophies.

The alternative and still undetermined points about ovarian function are:

1. Whether the ovary supplies one internal secretion or two internal secretions mutually antagonistic in character.

2. If the latter, whether one is derived from the stroma and one from the lutein cells, or both from follicular epithelium at different periods of activity.

It will be noticed that in the outline of menstruation, oestrus and ovulation and pregnancy so described no mention is made of any possible internal secretion derived from the uterus. The uterus is supposed to play a passive part, being entirely under the influence of the ovary in these processes.

The facts now established are:

1. That the endometrium has a secretion peculiar to the anoestrous state.

2. That there is evidence that some substance is elaborated by the pregnant uterus which stimulates the growth of corpora lutea in transplanted ovaries. We must, therefore, reconsider this matter, and I suggest that the ovary elaborates only one internal secretion having an influence on the uterus of an anabolic character, which at recurring intervals increases in amount and produces the phenomenon of pro-oestrus and oestrus.

A further formation of this substance occurs during pregnancy, owing to a stimulus derived from an internal secretion elaborated by the endometrium at the sites of the embedded trophoblasts, and provides for the increased growth of endometrium associated with the early stages of pregnancy, while the anoestrous or saline secretion of the uterus is antagonistic to the ovarian secretion, and during the anoestrous period overcomes the ovarian reaction, now reduced in intensity or amount.

Reference.

[1] *Journal of Physiology*, vol. xxii, No. 4; and *Lancet*, July 22nd, 1899.